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Integrative Etiopathogenetic Models of Psychotic Disorders: Methods, Evidence and Concepts

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Integrative models of the etiopathogesnesis of psychotic disorders are needed since a wealth of information from such diverse fields as neurobiology, psychology, and the social sciences is currently changing the concepts of mental disorders. Several approaches to integrate these streams of information into coherent concepts of psychosis are feasible and will need to be assessed in future experimental studies. Common to these concepts are the notion of psychotic disorders as brain disorders and a polythetic approach in that it is increasingly realized that a multitude of interindividually partially different pathogenetic factors interact in individual persons in a complex fashion resulting in the clinical symptoms of psychosis.

Key words: schizophrenia/disease concepts/classification

Introduction

Integrative models of the etiopathogenesis of psychotic disorders play a great role in the current discussions about the revision of the international classification systems of mental disorders, ie, the International Classification of Disorders (ICD-10) published by the World health organization[1] and the *Diagnostic and statistical manual of Mental disorders, Fourth Edition,* (DSM-IV) of the American Psychiatric Association.[2] This discussion is fueled by the enormous increase of knowledge in research into the causes of mental disorders. Modern integrative models of psychosis are usually grounded in the assumption that psychotic disorders are brain disorders and that a multitude of pathogenetic factors interact in individual persons in interindividually different combinations (polythetic approach).

Methodological Issues

According to DSM-IV (Text revision), the core symptoms of psychotic disorders are hallucinations and delusions, but no singular generally accepted definition exists and additional clinical features like disorganization, catatonia, loss of ego boundaries, impairments in reality testing, and others may be included.[2] ICD-10 states that "psychotic … simply indicates the presence of hallucinations, delusions, or a limited number of severe abnormalities of behavior, such as gross excitement and overactivity, marked psychomotor retardation, and catatonic behavior."[1] Thus, the core symptomatology is identical between both classification systems, but the definitions are different and ambiguous. The core symptoms of psychosis are found in a variety of mental disorders. Obviously, the causes of hallucinations and delusions are manifold. Most likely, these symptoms are but the common final symptomatic presentation of the diverse causes and mechanisms of maldevelopment, damage, or impairment of mental faculties. The substrate of these physiologic mental faculties and the place of action of the pathophysiologic factors is the brain with its intricate networks of interconnected neurons. Methodologically, a logical first step to construct integrated models of psychoses would be to describe the range and type of the pathophysiologic factors in these disorders.

Some genetic factors seem to act across classical diagnostic boundaries. Modelling their modes of action will be a major task. Major issues to consider are the time-variable phenotypic presentation of symtoms, the variable response to treatment, the multitude of confounding genetic and socioenvironmental risk factors, and the large number of putative interactions between these factors. Initial approaches with Discrete Event Simulation show that such analyses are feasible in complex mental disorders like schizophrenia, but these analyses have not yet focused on pathophysiology.[3] Structural Equation Modelling (SEM) may be helpful to model the complex interactions of genes, physiological functions as assessed by network analyses, and socioenvironmental factors. Some examples from psychotic disorders exist

which demonstrate the feasibility of this approach.[4] SEM was useful to model the clinical spectrum of psychotic symptoms and identified 5 major constituents in a large sample of healthy adolescents as a basis for a further long-term follow-up looking into predictive factors of the development of schizophrenia.[4] Hall and coworkers[5] used SEM in schizophrenia research when assessing the individual contributions of genetic factors to the expression of neurophysiologic endophenotypes. The method was also used to assess the determinants of social functioning in schizophrenia-related disorders.[6] The strength of this approach is that the relative contribution of various factors can be quantified.

Biological Models of Psychotic Disorders

Genetic investigations have provided ample evidence for a large number of genes, which are associated with an increased risk of developing schizophrenia or related psychotic disorders. However, the genetic contribution to the pathogenesis appears to be small. A number of these risk-conferring genes seem to increase the risk of a psychotic disorder in general rather than the risk for a specific psychotic disorder. While most genes associated with an increased risk of psychotic disorders code for proteins with a role in myelination, synaptic transmission, ion channel functions, or transcriptional regulation, some new analyses also showed an involvement of genes of lipid metabolism, cell development, or posttranslational RNA modification. Genome-wide analyses have also shown that the genetic background of schizophrenia is complex. A new aspect was the discovery that in some cases of schizophrenia, genetic "copy number variations" play a role, which are often caused by larger chromosomal deletions. This indicates a pathophysiologic role of the genes located in the deleted regions in schizophrenia.[7] Another new approach is the study of epigenetic regulatory phenomena in the pathophysiology of mental disorders, which lead to the discovery of pathways between prenatal and perinatal insults and the subsequent development of mental disorders in later life.[8] The insults include "psychosocial" factors like social defeat stress, which can induce epigenetic processes leading to microstructural alterations in the nucleus accumbens of experimental animals.[9] Such epigenetic processes are now held to be the primary pathophysiologic pathway for gene-environment interactions.

This brings up the question of the pathophysiology of structural and functional alterations of brain circuits in schizophrenia and related psychotic disorders. Regarding structural alterations, brain neuroimaging has only shown small degrees of atrophy in people with schizophrenia. Microstructural brain tissue changes found in schizophrenia are manifold, widespread, but at best very slight.[10] The findings are suggestive of an early neurodevelopmental abnormality affecting neuronal migration, survival, and connectivity.[11] In functional neuroimaging, no single brain center for hallucinations or delusions was identifiable, but a variable contribution from a range of networks and structures including the secondary association cortex, frontal areas, the cingulate gyrus, and subcortical structures was found[12] Functional magnetic resonance imaging and electroencephalography (EEG) mainly showed functional dysconnectivity between brain areas indicating white matter dysfunction, which would be explainable by synaptic dysfunction or axonal conduction deficits. For the latter, dysfunctions of the myelin-forming oligodendrocytes may play a role which could lead to a decrease of axonal action potential propagation speed. Accordingly, subtle histomorphological changes of oligodendrocytes have been found in the brains of people with schizophrenia postmortem.

The subtle structural but clear functional alterations of brain networks in schizophrenia make functional brain investigations centerstage in schizophrenia research today. Relatively stable functional findings have been obtained with evoked potential studies of the brain in people with schizophrenia. Task related investigations have been complemented recently by investigations of the "default mode" brain network, which is an ordered brain activity in the resting state. However, no common disturbances have been identified in people with psychotic disorder.[13] Brain network analyses in schizophrenia show a rather complex picture.[11] They support the opinion that there are many ways of disturbances of brain functional circuitry that may lead to the clinical picture of psychotic disorders.

Obviously, there are several functional units of the brains which themselves or in their connectivity with other functional brain areas may be disturbed in order to cause symptoms of psychosis. A way to analyze the complex picture of altered brain networks in schizophrenia is to identify functional brain units or "modules" as the objects of damaging factors.[14] Novel methods of data analysis like "graph theoretical analysis" provide quantifiable network properties and have consistently shown disturbed brain networks in patients with schizophrenia and other mental disorders (further discussed below).[15,16] One of the strongest pillars of our knowledge about the pathophysiology of psychotic disorders is the hyperdopaminergic state in the brains of people with schizophrenia. Antipsychotic drugs work by blocking this hyperdopaminergic state. Based on these observations, models of psychotic disorders were developed which assume that reduced "filtering" of new information is a central pathophysiologic aspect of psychotic disorders (aberrant salience).[17] Cognitive dysfunctions like "jumping to conclusions" are partly explained by increased level of dopamine at the synaptic cleft.[18] Whitford and colleagues presented an interesting unifying hypothesis with hyperdopaminergic neutrotransmission as a final common pathway of the pathophysiology of psychotic disorders.[19]

In schizophrenia, abnormal myelination of frontal white matter fascicles and resulting conduction delay in efference copies are hypothesized to play the central role in the pathway leading to the dopamine dysfunction by causing prediction errors (which leads to increased midbrain dopaminergic activity).[20] The theory combines information from both biological and psychological models of schizophrenia and makes a range of predictions, which can now be tested empirically. One of the strongest predictions would be that medication-fostering myelination should be able to ameliorate the symptoms, but such medication is currently not yet available.

Psychological Models of Psychotic Symptoms

Dysregulations of brain networks lead to cognitive dysfunctions, which may be enhanced by "premorbid" low intelligence in the case of schizophrenic disorders (cognitive reserve hypothesis).[21] While some cognitive functions are similarly disturbed in a range of mental disorders, some like working memory and executive functions are specifically altered in people with schizophrenia and their first-degree relatives compared with people with bipolar disorder.[22] Beyond such basic cognitive factors in psychotic disorders, more specific cognitive mechanisms have been assumed in the pathophysiology of hallucinations and delusions. Besides altered reality monitoring and filtering of new information as described above, these include cognitive misattribution of internal process to external sources or hypervalent cognitive schema, implicit association with negative self judgments, jumping to conclusions, intolerance against ambiguity, attentional shifts, abnormal perception, abnormal beliefs, aberrant salience, aberrant Bayesian inferences from prediction errors, and many more.[23] Such models have only been partly examined in people with psychotic disorders and different combinations of such factors seem to play a role in individual cases.

Social Models and Models of Environmental Factors of Psychotic Disorders

These models are discussed together here because there has been a trend in recent years to define pathophysiologic factors, which may be common to both. As pathways of pathophysiology initiated by social or other environmental factors often converge onto epigenetic factors and epigenetic mechanisms seem to provide an elegant way to understand gene-environment interactions, this area of research has gained much interest. Especially, prenatal immune challenges like infections have been shown in animal models to result in changes of brain networks and brain functions later in life. The individual contribution of social and environmental factors appears to be much larger than for the genetic factors. However, major methodological problems arise as social and environmental factors are often not easily objectively measured. Observer bias and prejudiced concepts of mental disorders may play an important role in some concepts and "trauma" is just one example of such a problematic conceptualization. Phillips and coworkers[24] recently reviewed the limitations of "life event" research especially regarding the concept of "stress", which plays an important role in the discussion about the pathophysiology of mental disorders. For clarity, it seems appropriate to differentiate between pre/perinatal factors and those of childhood and early adolescence. Several prenatal/perinatal factors have been identified as predisposing to psychoses. These are a higher parental age at the time of conception, perinatal hypoxia, fetal malnutrition (especially folic acid deficiency), maternal infections during pregnancy, and maternal stress. During childhood and adolescence, chronic stress, an urban environment, and a biographical background with migration and drug abuse (including cannabis) were identified as risk factors.[25] All these factors have in common that they activate epigenetic cascades, but the pathways from these cascades to psychotic symptoms are still unexplored. Thus, although epidemiological studies are quite clear, the pathophysiological mechanisms are still to be elucidated. Similarly, how social factors lead to psychotic symptoms is not known yet.

An important step in the elucidation of the mode of action of environmental factors was the discovery that many of these factors converge onto poor socioeconomic status as the decisive variable. Parental communication styles, hierarchy effects, cognitive factors, and many others seem to be involved in the mediation of the effects of a low socioeconomic status on brain development, brain function, and the development of mental disorders.[20] Although psychotic disorders have not yet been studied in these empirical analyses, such findings are of high interest for the development of concepts of psychotic disorders. Such empirical analyses are of great relevance for developing novel concepts of integrated models of psychoses, even though the development of schizophrenia has not been investigated regarding the role of socioeconomic deprivation.

An approach described by Bentall and Fernyhough[26] postulates that factors like unsecure binding or early childhood traumatization may lead to increased expectancy of threats when combined with a negative picture of oneself or a tendency to search for external causation. A tendency toward jumping to conclusions may add to the incipient paranoid development. These factors have been shown to play a role in the pathophyisiology of paranoid ideations and such approaches integrate biological, psychological, and social factors in the pathophysiology of mental disorders.[27]

Integrative Models

Only few integrative models of schizophrenia were developed with the explicit aim to explain the pathophysiology

and symptomatology using more recent findings from empirical investigations. One early attempt of great influence was the "two-hit hypothesis" which used a genetic vulnerability as the first step and subsequent other pathophysiologic influences (biological, environmental, psychological, or other) as the necessary "second hit" in the pathophysiology of schizophrenia.[28] Factors predisposing to the development of schizophrenia and factors precipitating its onset may be distinguished. An integrated model based on sociodevelopmental factors involved in the pathophysiology of psychosis was proposed.[29] These approaches were extended in the "three hit model" to include neurodegenerative factors which were thought to be induced or accelerated by the disease onset itself (ie, developmental risk factors, precipitating factors, and neurodegenerative factors[30]). These hypotheses have gained much empirical underpinning in recent years and can now be refined in that the pathophysiologic factors involved in each of the different "hits" are beginning to be elucidated as interactions of time variable and partly overlapping factors. The theoretical mechanisms for such multiple pathophysiologic factors interacting on the functions of a certain brain region have been described in an example using the prefrontal-limbic system in schizophrenia by Radulescu.[31]

The central idea of Howes and Kapur[32] is that multiple risk factors for psychoses like frontotemporal dysfunctions, genetic factors, prenatal infections, stress, and drugs may lead to a common final pathway of presynaptic hyperdopaminergic dysfunction. Gene-environment interactions could be integrated in this model via epigenetic regulation of genes of dopamine metabolism. In this model, aberrant salience is thought to be the consequence of the hyperdopaminergic state (although it is unclear how hyperdopaminergia leads to aberrant salience), and this is thought to be the decisive psychological function involved in the pathophysiology of psychotic symptoms. Psychosis is viewed as dopamine-driven aberrant salience filtered through the individual's cognitive and sociocultural schemas. The exact diagnosis within the psychosis spectrum reflects the nature of the pathogenic "hits" on the dopamine system coupled with sociocultural factors leading to dopamine pathways as the common final pathways. The kind of relationship between the hyperdopaminergic synaptic state and ensuing symptoms is still not elucidated. Current research in this area focuses on the validation of a salience assessment scale[33,34] and empirical investigations in patients with schizophrenia mainly reduced salience network connectivity,[35] a correlation between volume reduction in a brain salience network and the clinical phenomenon of reality distortions in patients with schizophrenia,[36] an inverse correlation of salience coding and negative symptoms,[37] and a correlation of aberrant salience with the presence of delusions in schizophrenia.[38] It remains to be determined whether these factors only operate in the pathway to schizophrenia or also in pathways leading to nonschizophrenic psychotic disorders.

In a similar model, Van Os and Kapur[17] developed a model of schizophrenia which emphasizes the interaction of gene and environmental factors and which regards schizophrenia as one aspect of a spectrum of psychotic disorders with gradually different degrees of manifestation of psychopathological symptoms (psychotic symptoms, negative symptoms, cognitive disorder, depression, and mania). Compared with the former model, this second model extends to schizoaffective and bipolar affective disorders, and it also discusses the differential roles of certain genetic factors for the different phenotypic pathways. This model is prototypic of the "spectrum" approaches using in this case, a complex analysis of 5 symptom dimensions to order the multitude of psychotic phenomenology. The advantage is clearly that not only schizophrenia but also other psychotic disorders are being included. The empirical basis for this model is still small.

Although not a completely integrated model, conceptualizing psychotic disorders by dimensions of symptoms instead of using categorical approaches also play a role in the current discussion about the revision of the psychiatric classification systems, especially the DSM-IV of the American Psychiatric Association. The evidence of epidemiological studies shows a continuum of psychosis-like experiences in the population, but some categorical aspects also apply, ie, a "psychotic" population can be distinguished.[39] As to the role for classification purposes, Craddock and Owen[40] discussed a spectrum model that is based on the observation that several genetic risk factors are shared between different types of psychotic disorders like schizophrenia and bipolar disorders. The degree of severity of the presented symptoms is regarded as a continuum with considerable overlap of symptomatology between different mental disorders. Gene-environment interactions could be essential modifiers and determinants of individual phenotypic expression of psychotic disorders. This leads to the proposal that future classification systems should be based on an assessment of the pattern and degree of pathophysiologic symptom dimensions rather than on categorical definitions. Also, psychiatric classification should more heavily rely on knowledge about the neurobiological foundations of the pathophysiology of psychotic disorders. The genetic data also make the inclusion of some genetic forms of mental retardation or autismus-spectrum disorders into any model of psychotic disorders necessary because there is genetic overlap of schizophrenia with this part of the spectrum of mental disorders.

For integrative models of psychotic disorders, the central question arises, which are the substrates of the actions of genetic, psychological, or environmental factors in the pathophysiology of the symptoms of psychosis. Implicit in the beforementioned models is the assumption that neuronal brain cells or their interactions

Table 1. Empirical Evidence for Disturbed Modularity in Patients With Schizophrenia

Key Findings	Method	Reference
Reduced local clustering and integration of functional networks in a working memory task in people with schizophrenia (n = 20)	Task-related EEG, graph theoretical analysis	44
Disrupted small-world network topology in people with schizophrenia (n = 31): increase of path length and decrease of connectivity correlated with illness-duration.	Resting-state fMRI, graph theoretical analysis	41
Significantly reduced modularity in childhood-onset schizophrenia (n = 13) due to reduced densitiy of intramodular connections between neighboring regions	Resting-state fMRI, graph theoretical analysis	43
Lower clustering and shorther pathlengths in patients with schizophrenia (n = 40)	Resting-state scalp EEG	45
Less hierarchical organization of brain network in schizophrenia (n = 203), increased mean connection distance and increased clustering	Structural MRI, interregional correlation of gray matter volume	46
Longer node-specific pathlengths and less centrality in frontal hubs in people with schizophrenia (n = 40)	Diffusion tensor imaging and magnetization transfer ratio assessment of brain MRI, graph theoretical analysis	47
Decreased strength of functional connectivity, reduced clustering and small-worldness in people with schizophrenia (n = 12)	fMRI functional connectivity and functional network metrics analyses	42

Note: EEG, electroencephalography; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging.

are this central target. Our group proposed a conception of mental disorders in which brain modules are postulated to be the substrates of the damaging factors.[14] ''Modular psychiatry'' rests on the assumption that the physiologic functions of such modules can be defined and measured, that their disturbances in mental disorders can be detected and quantified, and that it can be shown how such disturbances lead to the signs and symptoms of mental disorders. In modular psychiatry, mental disorders are thus based on empirically studied dysfunctions of neuronal circuitry. Such dysfunctions could be modified by gene-environment interactions and epigenetic regulation of neuronal development, maintenance of synapses, and myelination of long-tract association fibers of the brain. Currently, evidence is accumulating by several ways of investigations like EEG and magnetic resonance tomography that such brain modules exist, that they can be identified and analyzed, and that their interactions and hierarchical organization are altered in people with schizophrenia and other mental disorders like Alzheimer's disease and attention-deficit/hyperkinetic disorder[15,41].

Altered modularity will reveal itself as decreased or increased centrality (hubness), altered pathlengths, or altered correlation coefficients between brain areas. These alterations lead to a disturbed hierarchical architecture of the human brain modules, and such changes have been associated with cognitive factors and disease course characteristics in people with schizophrenia[41,42] including adolescent adults with childhood-onset schizophrenia.[43] The currently available empirical evidence for the modular approach is summarized in table 1.

The next step would be to determine how such altered brain network architectures lead to psychotic symptoms and whether similar alterations of brain modularity and other network characteristics can also be found in persons with nonschizophrenic psychotic disorders, eg, like in Alzheimer's disease or in cases of encephalitis. Such studies are now feasible since methods are available to use modularity analysis in EEG and magnetic resonance imaging (MRI) data. Modules of the brain could become the bridge between the levels of genetic risk factors, functional and structural brain imaging, brain network analyses, and clinical symptoms. However, currently the pathophysiologic mechanisms by which genetic factors and other somatic factors exert their influence on brain modules—or are influenced by mental disorders—are only beginning to be determined. It is still unclear, which brain modules are the targets in individual cases and how this leads to clinical symptoms. The workplan would thus involve firstly an identification of the disturbed modules, a characterization of the kind of disturbances, and the operationalization of methods like MRI or EEG to detect such disturbances. In further studies, it would then need to be shown that the amelioration of such disturbances is measurable and correlates with

significant clinical improvements. Then, the assessment of module disturbances could become a key asset for a "modular psychiatry" based on the objective determination of neurophysiological dysfunctions. In modular networks, the frontal lobe may play a central role in controlling behavior (reviewed by Seitz and coworkers[48]).

A central aspect of modular psychiatry is the communication between different brain areas, which basically relies on synaptic neurotransmission. McGlashan and Hoffman[49] provided a seminal neural network model of schizophrenia based on synaptic loss and reduced cortical connectivity, which has considerable attractiveness because it leads to spontaneous network acitivity simulating hallucinations, is well in accordance with some experimental findings and provides a unifying framework with testable hypotheses.

In conclusion, all 4 integrated models are based on complex gene-environment interactions with a range of propsychotic factors being combined in individually different constellations to lead to psychotic disorders. A common theme is the conceptualization of a final pathway leading to the disturbance of neural modules in a yet unknown manner, which is accompanied by or leads to a hyperdopaminergic synaptic state. The strengths of these models are their empirical foundations especially in genetic or neurophysiologic studies. This may hopefully lead to objective and quantifiable analyses of the individual risk factors, their interactions and role in the pathophysiology of psychotic symptoms. While several pathophyiologic risk factors may be shared among all persons affected by psychotic disorders, others may play a role only in individual cases. Modular psychiatry combined with quantitative modeling methods may lead to quantified assessments of the kind, directions, and time-variability of interactions of pathophysiologic factors in individual networks of psychotic pathophysiology explaining not only the current symptomatology but also explaining disease courses and providing prognostic information. This should be helpful not only for the purposes of diagnosis and classification of psychotic disorders but also for individualized treatment approaches. Disadvantages are the yet small evidence base and the complexity of the putative interactions with a multitude of interindividually and probably even time-variant pathophysiologic factors. Currently, there is no empirically validated integrative model of all aspects of psychotic disorders, but modular psychiatry with its clearly operationalized definitions and empirical testability holds promise as a useful basis for further investigations in this research area.

Classification of Mental Disorders in DSM-5 und ICD-11

Currently, the psychiatric classification systems ICD-10 and DSM-IV are being revised including the chapter on psychotic disorders. One of the major conceptual issues is whether a novel metastructure can be initiated and one suggestion is to cluster groups of similar mental disorders in groups defined by a set of similarity criteria (table 2)[50,51].

Table 2. Criteria for the Similarity of Mental Disorders for Clustering for the Proposal of DSM-5[50]

1. Common genetic risk factors
2. Familiality
3. Common environmental risk factors
4. Common neural substrates
5. Common biomarkers
6. Common temperamental antecedents
7. Common cognitive or affective processes
8. Similar symptoms
9. High rates of comorbiditay
10. Similar disease course
11. Similar treatment response

Note: DSM-5, *Diagnostic and statistical manual of mental disorders, Fifth Edition*

The relative importance of these factors and how to assess them are questions, which beg standardization and clear operationalizations. Until such novel metastructures are available, the concept of "schizophrenia" still has clinical utility. However, the concept needs to be better integrated into neurobiological findings and a major research initiative is currently underway to determine these neurobiological foundations.[52] The putative results may not only improve the classification of mental disorders but also the conceptualization of psychotic disorders.

In conclusion, several integrated models of psychotic disorders are now available and testable in clinical situations. The further development of these models and their role in developing novel diagnostic and therapeutic strategies will hopefully lead to a better understanding and optimized modes of diagnosis and therapy of psychotic disorders.

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